Corticosteroids in Neonatology: Postnatal Corticosteroids in Preterm Infants with Bronchopulmonary Dysplasia

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Introduction

Adequate pulmonary function is crucial for preterm infants. In addition to being structurally immature, the preterm lung is susceptible to injury resulting from different prenatal conditions and postnatal insults. Lung injury may result in impaired postnatal lung development, contributing to chronic lung disease, and many preterm infants who survive go on to develop this pathology. This is probably caused by persistent inflammation in the lungs, and thus chronic lung disease is a major problem for infants in neonatal intensive care units and is associated with higher mortality rates and worse long-term outcomes in survivors.

Chronic lung disease after preterm birth, also known as bronchopulmonary dysplasia (BPD), a major morbidity of the very preterm infant, is remarkably resistant to therapeutic interventions, and negatively affects neurodevelopmental outcomes. There is a complex interaction between lung injury, lung inflammation, lung repair, and altered lung development. Also, there are interactions between fetal, perinatal, and postnatal factors modulating lung injury.

Neonatal Lung Injury

Preterm birth is greatly associated with respiratory distress syndrome (RDS), caused by structural and functional immaturity of the newborn lung. In addition to simple structural immaturity, the preterm lung is susceptible to injury resulting from different prenatal conditions such as intrauterine growth restriction or oligohydramnios, genetic disposition, transition at birth, and postnatal procedures and insults such as

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R. Cimaz (ed.), *Systemic Corticosteroids for Inflammatory Disorders in Pediatrics*, DOI 10.1007/978-3-319-16056-6_14

mechanical ventilation–induced trauma from volume and pressure changes, extension of tissue and oxygen toxicity, sepsis, hypoxia, and others. These early alterations may interfere with lung development and therefore exert lasting effects on pulmonary plasticity and integrity, finally resulting in structural and functional impairment. Although growing experimental evidence can elucidate the link between lung injury, lung inflammation, lung repair, and altered lung development, the interactions between injurious insults and inflammatory stimuli on different levels are complex and remain to be fully understood [1]. Furthermore, recent findings support the hypothesis that chronic lung injury originating in this early period of life or even antenatally may indeed have long-term adverse respiratory effects, and studies report an association between chorioamnionitis and both recurrent wheezing and physician-diagnosed asthma [2]. In addition, young adult survivors of moderate and severe BPD may be left with residual functional and characteristic structural pulmonary abnormalities, most notably emphysema. The premise is that extremely preterm infants may have immature adrenal gland function, predisposing them to a relative adrenal insufficiency and inadequate anti-inflammatory capability during the first several weeks of life.

Benefits of Corticosteroids in Lung Inflammation

Since persistent inflammation of the lungs is the most likely cause, corticosteroid drugs have been used to either prevent or treat chronic lung disease because of their strong anti-inflammatory effects particularly in babies who cannot be weaned from assisted ventilation. The beneficial effects were a shorter time on the ventilator and less chronic lung disease, but the adverse effects included high blood pressure, bleeding from the stomach or bowel, perforation of the bowel, an excess of glucose in the bloodstream, and an increased risk of cerebral palsy at follow-up. There were significant benefits for the following outcomes: lower rates of failure to extubate and decreased risks of chronic lung disease at both 28 days' and 36 weeks' postnatal age; death or chronic lung disease at 28 days' and 36 weeks' postmenstrual postnatal age; patent ductus arteriosus; and retinopathy of prematurity, including severe forms of this condition. There were no significant differences in the rates of neonatal or subsequent mortality, infection, severe intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, or pulmonary hemorrhage. Gastrointestinal bleeding and intestinal perforation were significant adverse effects, and the risks of hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure were also increased.

Neurodevelopmental Outcomes

Long-term follow-up studies [3] report an increased risk of abnormal neurological findings and cerebral palsy. However, the methodological quality of the studies determining long-term outcomes is limited in some cases; the surviving children were assessed predominantly before school age, and no study was sufficiently

powered to detect important adverse long-term neurosensory outcomes. There is a compelling need for the long-term follow-up and reporting of late outcomes, especially neurological and developmental outcomes, among surviving infants who participated in all the randomized trials of early postnatal corticosteroid treatment. Dexamethasone was used in most studies, and only few used hydrocortisone. In subgroup analyses by type of corticosteroid, most of the beneficial and harmful effects were attributable to dexamethasone; hydrocortisone had little effect on any outcomes except for an increase in intestinal perforation and a borderline reduction in patent ductus arteriosus. Hydrocortisone appears to have less neurological impact than dexamethasone, even with adjustment for dose equivalency [4].

There are certain biological differences between these agents that may be of neurological relevance. Hydrocortisone differs from dexamethasone as it has both mineralocorticoid and glucocorticoid actions. In animal models, dexamethasone, which binds only to glucocorticoid receptors, induced neuronal degeneration within the hippocampus. In humans, alterations in hippocampal volume and synaptic plasticity and associative memory were reported with dexamethasone in preterm infants [5]. High-dose postnatal dexamethasone treatment for BPD was associated with decreased brain volumes on magnetic resonance imaging at 18 years of age, specifically total brain tissue, cortical white matter, thalamus, and basal ganglia nuclei. Surprisingly, some studies found no significant differences in the hippocampus or cerebellum, which are brain areas with very high concentrations of glucocorticoid receptors. Even in the absence of significant postnatal medical sequelae, preterm birth has a profound effect on neuroanatomical structures in childhood and adolescence [6–8]. Some authors have reported that individuals born extremely preterm have smaller brain volumes than term-born controls at 18 years of age, including the hippocampus and cerebellum as well as other brain regions; other authors have reported similar findings following preterm birth, including extremely preterm infants without "serious neurologic or medical conditions" at 7–10 years of age. They found that these children had smaller total brain volumes, white and gray matter volumes, and smaller basal ganglia and thalami than term-born controls [6–8]. These studies highlight the difficulty of distinguishing the effects of prematurity and its complications from the effects of a specific therapeutic intervention.

The differences observed in neurodevelopmental outcomes may result from the different effects of these agents on the hippocampus, an area of the brain critical for learning, memory, and spatial processing. The hippocampus contains a high density of both mineralocorticoid and glucocorticoid receptors. Hydrocortisone, which is identical to native cortisol, can bind to both classes of receptors. By contrast, dexamethasone binds only to glucocorticoid receptors, and in animal models this has been shown to result in degeneration and necrosis of hippocampal neurons.

It is also hypothesized that the longer biological half-life of dexamethasone relative to hydrocortisone influences potency and potential adverse effects, because it could have a much higher relative potency [9, 10].

Late steroid treatment (after 7 days of life) was associated with a reduction in neonatal mortality (at 28 days), but not mortality at discharge or latest reported age. Benefits of delayed steroid treatment included reductions in failure to extubate by 3, 7, or 28 days, chronic lung disease at both 28 days' and 36 weeks' postnatal age,

need for late rescue treatment with dexamethasone, discharge on home oxygen, and death or chronic lung disease at both 28 days' and 36 weeks' postmenstrual postnatal age. There was a trend toward an increase in risk of infection and gastrointestinal bleeding, but not necrotizing enterocolitis. Short-term adverse effects included hyperglycemia, glycosuria, and hypertension. There was an increase in severe retinopathy of prematurity, but no significant increase in blindness. The trends toward an increase in cerebral palsy or abnormal neurological findings were partly offset by a trend in the opposite direction in death before late follow-up, but the combined rate of death or cerebral palsy was not significantly different between the steroid and control groups [11].

However, key messages continue to resonate following these studies and the policy statement of the American Academy of Pediatrics is that high doses of dexamethasone (>0.25 mg/kg/dose or >1.0 mg/kg total) should be avoided owing to their adverse neurological consequences because of reduced brain volume and increased disability; low-dose dexamethasone (0.15 mg/kg/dose commence or total 0.9 mg/kg) may help extubation but does not improve survival or BPD, and it reduces brain volumes but does not increase early disability. Moreover, low-dose (1–2 mg/kg/day) and high-dose hydrocortisone (3–6 mg/kg/day) after the first week of life do not seem to increase neurological risk, but have not been shown to improve rates of survival without BPD. Despite this concern over efficacy and safety, and despite the uncertainty, systemic corticosteroids remain a common treatment in very preterm infants: Close to 7 % of all preterm infants receive dexamethasone and 7 % receive hydrocortisone. Clinicians need guidance in balancing the risks against the benefits because both BPD and corticosteroids are associated with adverse long-term neurologic outcomes: Lung disease itself, without any glucocorticoid therapy, results in anomalies in brain white matter development and BPD is also linked to adverse neurodevelopmental outcomes. In addition, BPD is highly variable; even within this diagnosis, it is likely that sicker babies are more often treated with dexamethasone, and those babies are also more likely to have worse outcomes.

Thus, a proper approach to the problem is to consider if the risks and benefits of corticosteroid treatment might vary with the underlying risk of developing BPD. To this end, data available from randomized controlled trials showed that the effect of systemic corticosteroids on the combined outcome of death or cerebral palsy was negatively related to the rate of BPD in the control group. Therefore, if the rate of BPD in the control group was low, the steroid treatment was harmful, while if the rate of BPD in the control group was high, there was benefit and an increased incidence of survival free of cerebral palsy. Thus, clinicians who need guidance on whether to start systemic steroid therapy in ventilator-dependent infants could use their own local data for the risk of BPD to identify the highest-risk infants who might have an actual benefit from treatment.

No randomized controlled trials of other systemic glucocorticoids, such as prednisone or methylprednisolone, to treat or prevent BPD have been published. Moreover, no additional evidence has been published to support the efficacy of inhaled glucocorticoids in preventing or decreasing the severity of BPD [11].

Conclusions

The benefits of *early* postnatal corticosteroid treatment (first 7 days of life), particularly dexamethasone, may not outweigh the adverse effects of this treatment. Although early corticosteroid treatment facilitates extubation and reduces the risk of BPD and patent ductus arteriosus, it causes short-term adverse effects including gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure. Long-term follow-up studies report an increased risk of abnormal neurological findings and cerebral palsy, but long-term outcome data are limited; the surviving children were assessed predominantly before school age, and no study was sufficiently powered to detect important adverse long-term neurosensory outcomes. There is a compelling need for the long-term follow-up and reporting of late outcomes, especially neurological and developmental outcomes, among surviving infants who participated in all the randomized trials of early postnatal corticosteroid treatment. The beneficial or the harmful effects of hydrocortisone are few, and it cannot be recommended for the prevention of chronic lung disease. Use of early corticosteroids, especially dexamethasone, to treat or prevent chronic lung disease should be curtailed until more research has been performed [12].

Postnatal *late* corticosteroid treatment for chronic lung disease initiated after 7 days of age may reduce neonatal mortality without significantly increasing the risk of adverse long-term neurodevelopmental outcomes, but the methodological quality of the studies determining the long-term outcome is limited and the surviving children were been assessed before school age, when some important neurological outcomes cannot be determined with certainty. Moreover, no study was sufficiently powered to detect increased rates of important adverse long-term neurosensory outcomes. On the other hand, postnatal late corticosteroid treatment at high doses is associated with short-term side effects such as bleeding from the stomach or bowel, higher blood pressure, and glucose intolerance.

Given the evidence of both benefits and harms of systemic postnatal steroidal treatment, it seems important to reserve the use of late corticosteroids for those infants who cannot be weaned from mechanical ventilation and to minimize the dose and duration of treatment. Considering the existing data, we believe that early postnatal corticosteroids are harmful and should not be further tested. Conversely, we should consider trials for infants who cannot be extubated by 14–21 days, who are at significant risk of developing BPD. Such trials must be large enough to measure the impact of steroids on both pulmonary outcomes and important long-term developmental outcomes. In fact, the American Academy of Pediatrics in 2010 stated that very low-birth-weight infants who remain on mechanical ventilation after 1–2 weeks of age are at very high risk of developing BPD. When considering corticosteroid therapy for these infants, clinicians might conclude that the risks of a short course of glucocorticoids to mitigate BPD are justified. This individualized decision should be made in conjunction with the infant's parents [13].

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